U.S. DEPARTMENT OF COMMERCE
National Technical Information Service

PB-251 611

AMITROLE ADVISORY COMMITTEE REPORT

DEPARTMENT OF AGRICULTURE

PREPARED FOR
ENVIRONMENTAL PROTECTION AGENCY

12 MARCH 1971

106076

PB 251 611

REPORT

of the

AMITROLE

ADVISORY

COMMITTEE

March 12, 1971

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U. S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

EPA-540/5-71-001

REPORT OF THE AMITROLE ADVISORY COMMITTEE

RECOMMENDATIONS

The Committee recommends continuation of the cancellation of registration of Amitrole for use on food crops as listed on Page 25 of the USDA Summary of Registered Agricultural Pesticide Uses (2nd Edition); it does not recommend reclassification of these listed uses as non-food uses.

INTRODUCTION AND BACKGROUND

Amitrole (Aminotriazole) was registered as a herbicide under the Federal Insecticide, Fungicide and Rodenticide Act in 1956. In 1958 Amitrole was registered for use on cranberry bogs after harvest. In 1957, 1958 and 1959 the herbicide was misused by being applied prior to harvest, and cranberries were found contaminated by Amitrole. In 1959 Amitrole was reported to be a highly potent goitrogen and to induce cancers of the thyroid of rats when it was contained in their diets. In 1963 the post-harvest use of Amitrole on cranberry bogs was withdrawn because detection of residues in berries was claimed by regulatory agencies.

In 1965 the National Academy of Sciences, National Research Council, at the recommendation of the President's Science Advisory Committee, appointed a Pesticide Residues Committee specifically to study the concepts of "no residue" and "zero tolerance" as they relate to pesticide use. The Committee recommended that the concepts of "no residue" and "zero tolerance," as employed in the registration and regulations of pesticides, are scientifically and administratively untenable and should be abandoned,

especially since continually improving analytical techniques are capable of detecting smaller and smaller residues. Based on the Committee's findings, the USDA and the DHEW published a joint statement in the Federal Register on April 13, 1966, providing that all uses of pesticides involving reasonable expectation of small residues on food or feed at harvest in the absence of a finite tolerance or exemption should be discontinued as of December 31, 1967. The joint statement led in February, 1968, to the cancellation of registration of Amitrole for all uses listed on Page 25 of the USDA Summary of Registered Agricultural Pesticide Chemical Uses. In May, 1969, the FDA, answering a petition, indicated that no finite tolerance could be established for Amitrole under the Federal Food, Drug and Cosmetic Act since it produces cancer in experimental animals.

The firms having registration of products containing Amitrole for use on food crops filed petitions (March, 1968) requesting that the matter be referred to an advisory committee as provided under Title 7, Chapter III, Part 364 of the Code of Federal Regulations. Under these provisions the National Academy of Sciences, National Research Council, was asked to suggest potential candidates for the Advisory Committee, and the Department of Agriculture then appointed the following individuals:

Dr. William A. Meissner, Chairman
Dr. Chester L. Foy
Dr. James G. Hilton
Dr. William B. House
Dr. Svend W. Nielsen

The Committee was requested to consider all relevant factors and submit a report and recommendations as to the registration of the articles (USDA Reg. No.'s 264-68, 264-124, 264-135, and 241-60) in Exhib-

BIBLIOGRAPHIC DATA SHEET	1. Report No. EPA-540/5-71-001	2.	3. Recipient's Accession No.
4. Title and Subtitle Report of the Amitrole Advisory Committee March 1971			5. Report Date March 12, 1971 6.
7. Author(s) Amitrole Advisory Committee -- see below for authors			8. Performing Organization Rept. No.
9. Performing Organization Name and Address William Meissner, Chester Foy, James Hilton, William House, Svend Nielsen			10. Project/Task/Work Unit No. 11. Contract/Grant No.
12. Sponsoring Organization Name and Address US Department of Agriculture, Washington, D.C.			13. Type of Report & Period Covered 14.

15. Supplementary Notes

16. Abstracts

The following items are discussed in this report, with regard to Amitrole: toxicology, plant physiology, persistence in soils, residue in food and feed crops.

17. Key Words and Document Analysis. 17a. Descriptors

Amitrole
herbicide
FIFRA
Aminotriazole
cranberry bogs
toxicity
plant physiology
soil persistence
residues in food and feed

17b. Identifiers/Open-Ended Terms

17c. COSATI Field/Group

18. Availability Statement	19. Security Class (This Report) UNCLASSIFIED	21. No. of Pages 21
	20. Security Class (This Page UNCLASSIFIED	22. Price $3.50

it 2, for use on food crops, together with all underlying data and a statement of the reasons or basis for the recommendations. Committee function began on November 16, 1970, when the Chairman acknowledged receipt of registrants' petitions and other exhibits. On January 7, 1971, an extension of 60 days for submission of the report was granted.

The Advisory Committee met in Washington, D.C., on December 16 and 17, 1970. After reviewing its charge, the Committee considered the Exhibits and References (Appendices 1 and 3)*. Presentations by the registrants were heard and discussed (Additional Exhibits--Appendix 2)*. Technical information and advice was obtained from representative members of the Pesticide Regulation Division, Environmental Protection Agency, and the Food and Drug Administration. The Committee concluded its two-day meeting in executive session with discussion leading to a concensus for recommendations. Further investigations were assigned to respective Committee members, and the meeting adjourned with the intent of handling future business by mail if possible. Mr. David L. Bowen of the Environmental Protection Agency, Pesticides Regulation Division, served as Committee Secretariat and kept notes of the meeting.

DISCUSSION

Toxicology

Amitrole administered orally to rats enters the blood through the gastro-intestinal tract and probably mostly through the gastric mucosa (R-1). It is fairly rapidly distributed throughout the tissues and eliminated through the kidneys. It inhibits liver and kidney catalase,

* E = Exhibit
R = Reference
AE = Additional Exhibit

liver peroxidase, and thyroid peroxidase. The site of metabolism is in the liver where a metabolite is formed which might be responsible for catalase inhibition since such inhibition persists even after Amitrole itself is no longer present (R-1).

In animal experiments Amitrole has shown a low acute toxicity after oral, intravenous or intraperitoneal injection (R-2). For example, the LD50 for mice after oral administration was found to be 14,700 mg/kg. There have been no long-term adverse effects in rats from chronic skin applications or chronic inhalation (AE-3).

Amitrole is a fairly potent antithyroid agent (R-3). The goiter production by Amitrole results from the inhibition of thyroid peroxidase which participates in the iodination reactions involved in the biosynthesis of thyroid hormone (R-4). The amount of inhibition is dose related. Diminished hormone output elicits an increased secretion of Thyroid Stimulating Hormone (TSH) by the pituitary which stimulates the thyroid to hyperplasia in order to synthesize at a more rapid rate. A compensated hypothyroidism as well as a goiter results. Fregley (AE-3g) reports that 0.5 ppm in food had no effect in the rat on any of seven separate measures of thyroid function studied. At 2 ppm in food, two of sixteen separate measures of thyroid function were affected significantly. Strum and Karnovsky (R-4) found early changes in the thyroid after administration of Amitrole for only one week and reduction in thyroid activity within three days. Most experimental goiters induced by Amitrole have been the result of long-term and continuous administration.

The Committee noted with interest that the ingredient designated as T in Cytrol Amitrole-T and Amitrol-T is ammonium thiocyanate. The name

ammonium thiocyanate is not included on the labels and apparently is considered as an inert substance by both the registrants and the Pesticide Control Division. However, the thiocyanate ion has in itself a goitrogenic effect and could be a contributing factor to the development of goiter, especially when intake of iodine is low (R-5). Thus, two of the four products involved (E-16) potentially have a double goitrogenic activity. Also, it is known that in plants ammonium thiocyanate potentiates and/or prolongs the persistence of Amitrole by slowing down its normal metabolic degradation (AE-6, AE-7). Whether such could also happen in animals is unknown, but the distinct possibility exists.

The carcinogenic effect of Amitrole was first reported in 1959 (E-9, E-10), subsequently by Russian observers (AE-3) and more recently by Innes et al (AE-3f). The Food and Drug Administration noted in 1959 that feeding high dosages of Amitrole stimulated abnormal growth of the thyroid gland (E-9). A summary of subsequent research conducted by American Cyanamid Company showed that, with chronic feeding studies in rats, thyroid tumors began appearing at the 68th week of feeding at 100 parts per million; after two years thyroid tumors were present in more than half of the rats examined which had been fed 100 parts per million. These tumors were diagnosed as various types of adenoma and carcinoma. At lower levels of feeding, 50 and 10 parts per million, thyroid tumors also appeared in decreasing number. A "no effect level" was not established (E-9).

Innes et al (AE-3f) in 1969 used Amitrole as a positive control against which carcinogenic activity of other pesticides and industrial compounds were compared. The Amitrole was administered at a daily

dosage of 1000 mg/kg. The Amitrole-fed mice were carried for 53 to 60 weeks with 64 of the 72 animals developing thyroid carcinomas and 67 of the 72 animals developing hepatomas.

The mode of action of Amitrole in producing thyroid tumors is presumably related to its goitrogenic effect and resultant TSH stimulation. Other antithyroid agents, such as thiouracil, produce experimental thyroid cancers in a similar manner through TSH stimulation of the thyroid and, in fact, TSH itself has produced thyroid tumors experimentally (R-6). In this sense Amitrole acts in a different manner from the classic carcinogenic hydrocarbons, such as methylcholanthrene, inasmuch as its effect is mediated by hormonal stimulation. It should be noted that in either type of carcinogenic stimulation, hyperplasia usually precedes neoplasia. The fact that Amitrole is carcinogenic because it induces exaggerated physiologic stimulation and hyperplasia makes it no less a carcinogen.

Plant Physiology

Amitrole is a herbicide, plant growth inhibitor, and defoliant. It is a foliarly-applied, readily translocated, nonselective spray chemical for control of annual and perennial grasses and broadleaved weeds (R-7, R-8). The major phytotoxic effect is to interfere in some presently unspecified way with the normal metabolism of purines, pyrimidines, nucleic acids and related compounds leading to the disorganization and inhibition of new, active growth (R-8, AE-9a). The appearance of chlorotic or albino tissue is the most striking symptom of Amitrole phytotoxicity. The typical chlorotic lesions result from the failure of plastids (self-replicating organelles rich in protein) to reproduce properly. Thus the effect of

Amitrole on protein appears to be indirect. Although similar biochemical lesions may be produced in different species, the particular lesion which is critical may be different for different organisms. Amitrole apparently attaches to amino acids and protein by forming a free radical and may become bound in an insoluble form.

The present method of analysis, developed by Storherr and Burke of FDA (AE-9) has a claimed sensitivity of 0.02 ppm for Amitrole and "all known metabolites." By this and other methods, "disappearance" from certain plant species has been reported. However, dissipation or removal from ready detection does not necessarily mean complete degradation. For example, the possibility that Amitrole was bound in insoluble form or was lost from roots, similar to other mobile herbicides, has not been critically evaluated.

Dalgaard-Mikkelsen and Poulsen (R-2) have emphasized (1) that attention not be confined to toxicity of original herbicide compounds, but should include the influences on plant metabolism which perhaps might lead to accumulation of endogenous products and (2) that little is known regarding toxicity of metabolites of herbicides formed either in soil or plants.

The triazole nucleus is highly stable; hence it is not surprising that conclusive evidence of ring cleavage under physiological conditions has not been reported. Rather, rapid metabolism of Amitrole in higher plants appears to be restricted principally to conjugation. Conjugation with other plant constituents has also been proposed. Technically, these conjugates are not "degradation" products because they still contain the intact triazole nucleus which may be regenerated by chemical treatment.

The Committee was impressed by the lack of detailed information available on the metabolites of Amitrole or ammonium thiocyanate, and on the influence of environmental and chemical factors on the metabolism in plants. For example, Smith et al (AE-7) reported that Amitrole metabolism in leaves of two species was more rapid in the light than in dark; also, at 28° C than at 15° or 22° C. In the same study, pre-treatment with benzyladenine enhanced metabolism, but ammonium thiocyanate markedly retarded or reduced metabolism of Amitrole, thus acting as a potentiator for Amitrole in plant tissues. Yet, the Committee was led to understand that virtually all of the earlier residue data reviewed in the case pertained to Amitrole alone, not Amitrole plus ammonium thiocyanate (Amitrole-T, which comprises two of the four commercial products under consideration).

Persistence in Soils

Since Amitrole is not applied directly to food crops, but to the soil in which these crops are grown, the question of the persistence and degradation in soils is of prime importance. In some soils the chemical disappears rapidly while in others the applied Amitrole may persist for months. The factors governing the rate of degradation of Amitrole are not satisfactorily understood at present. Sund (R-9) reported that Amitrole becomes tightly bound to soil particles and has a tendency to complex with metals. Ashton (R-10) and Ercegovich and Frear (R-11) have also reported the complexes of Amitrole with metals. Several investigators (R-10, R-11, R-12) have proposed that soil microorganisms are responsible for the degradation of Amitrole, but have not been able to isolate or identify the microorganisms responsible. More

recently Kaufman et al (R-13) have reported that the degradation of Amitrole in soil is largely a chemical process only indirectly related to microorganisms. Plimmer et al (R-14) have studied the reactions of Amitrole in several isolated systems and propose the decomposition of this substance by free radical-generating systems. These investigators have proposed the breakdown of Amitrole to carbon dioxide, urea and cyanamide. In light of these different possibilities for the degradation of Amitrole, it is not surprising that the persistence of the chemical appears to vary greatly with the soil type and composition. For example, the Herbicide Handbook (R-7) reports a duration of two to three weeks in warm, moist soils while Riepma (R-15) has reported that two thirds of the applied Amitrole remained after 60 days in high clay, low organic matter soil.

The degradation of Amitrole by either microorganisms or by free-radical generating systems raised questions about the persistence and fate of this chemical in surface waters. There appears to be a lack of information about this area. The Committee could visualize situations where high concentrations of Amitrole might be present in surface waters either from run-off or from treatment of weeds growing on the banks of ditches and dikes.

Under these conditions information about the toxicity of this substance on marine life and other wild life that might be ingesting the water would be essential. This would be particularly true if the Amitrole persisted in the surface water for any period of time and was transported from location to location by the water.

Residue in Food or Feed Crops

The current method of analysis for Amitrole residues (Storherr and Burke) has claimed sensitivity of 0.02 ppm and is said to account not only for Amitrole, but also all known metabolites of Amitrole in plant tissue (AE-9). Amitrole is picked up from soil and is systemic in plants so while it is not used directly on food or feed crops, its close proximity to such crops raises the question of potential residue. Amitrole is no longer registered for use on cranberries, but the ability of the chemical to be retained in plants was demonstrated by Onley (R-16) who found residues in the berries harvested 12 months after application. Other investigators using direct application of radioactive C^{14} Amitrole to corn plants (E-15) and tokay grapes (R-17) have reported detectable radioactivity 45 days and 112 days after treatment.

From current registered uses of Amitrole and when used according to directions, no reports of residues in food or feed crops have been demonstrated in abundant residue data. Market-basket surveys since 1964 have not shown detectable residues in crops grown on land treated with Amitrole.

Other Items

The Committee was presented with voluminous material for consideration, consisting of oral and written reports, copies of correspondence, reprints, etc. (See Exhibits). While all of this material was studied by the Committee, only the more pertinent items leading to the Committee's conclusions have been discussed above, and no attempt has been made to cite each reference and report.

Amitrole is a highly effective herbicide of considerable agricultural importance. It has been widely used for over a decade, and no evidence was presented to the Committee that Amitrole, used as now registered, has had any harmful effects on man or animals. Available data indicate no detectable residues on food products when it is used as currently registered. The 1968 decision to cancel registration, which the Committee has been asked to arbitrate, was based on reevaluation of policy, rather than on new evidence of residues or harmful effects. The Committee was particularly concerned that both the reevaluation of policy and Committee deliberations were partially dependent on usage of scientifically vague terms such as, "reasonable expectation of residues"; and "applications highly remote from food crops." If such terms were more specifically defined, actions of this and future committees would be sharpened.

The Committee, however, also appreciates that Amitrole has been accepted as a carcinogen. Although it seems highly unlikely that Amitrole could contaminate a human diet in sufficient quantities to produce cancer, the carcinogenicity of the chemical must necessarily influence the conclusions and recommendations of the Committee. This is evident in the following statements:

(A) Section 409 (348) (c) (3) (A) of the Federal Food, Drug and Cosmetic Act, as Amended (R-18): "No additive shall be deemed safe if it is found to induce a cancer when ingested by man or animal . . . "

(B) FDA, 1959 (E-9): "It has not been determined scientifically whether it is possible to establish a safe level of use for a carcinogen in human food."

(C) A. H. Fleming, Secretary of HEW, 1959 (E-7): "The FDA has declined to set any tolerance for any amount of a chemical in foods if the chemical produces cancer when fed to test animals. This principle is set down in the Food Additives Amendment enacted last year in a specific provision prohibiting the FDA from setting any tolerance for any such chemical.

"While in theory there may be a minute quantity of a carcinogen which is safe in foods, in actuality our scientists do not know whether this is true or how to establish a safe tolerance."

(D) Pesticide Residues Committee, 1965 (E-11): "Although it is reasonable to assume that a no-effect level could be demonstrated for a compound with respect to carcinogenic potential, approval of such a compound for use when it might leave a residue on food would require most extraordinary justification."

(E) Pesticide Program, USPHS, 1969 (E-13): "We cannot recommend reregistration of this Reg. No. [Amitrole] because we do not believe that a compound which produces cancer in experimental animals should be employed as a pesticide."

(F) Secretary's Commission on Pesticides and their Relationship to Environmental Health, 1969 (E-14): "It is recommended that the exposure of human beings to pesticides in this Category "B" [includes compounds judged "positive" for tumor induction and specifically mentions Amitrole] be minimized and that use of these pesticides be re-

stricted to those purposes for which there are judged to be advantages to human health which outweigh the potential hazard of carcinogenicity."

In the present climate of ecologic concern, with such policy statements made by statute, agencies and committees, as above, the Committee feels that it would be difficult to recommend continued use of an accepted carcinogen, even if no residue has been demonstrated.

While the available residue data on Amitrole indicate that when used according to current registrations and directions no residues have been detected, it is clear that the USDA (EPA) feels that there is a reasonable expectation of some level of residues in harvested crops.

The Committee, as noted above in discussion, was concerned by the relative lack of information, not of tests for residual Amitrole, but regarding its metabolism, metabolites, degradation and ultimate fate in soils, plants and water.

Despite the fact that Amitrole is not registered for direct spray on crops and label directions call for spraying on the soil before planting or when no fruit is present, the Committee does not feel that such applications can be considered as "remote" from food crops. It does not seem to the Committee that with existing knowledge it is possible to conclude dogmatically that there is no "reasonable expectation" of a residue, even though no residues have been demonstrated using current analytical techniques.

Because of these considerations, the Committee unanimously adopted the following recommendation:

> The Committee recommends continuation of the cancellation of registration of Amitrole for use on food crops

as listed on Page 25 of the USDA Summary of Registered Agricultural Pesticide Uses (2nd Edition); it does not recommend reclassification of these listed uses as non-food uses.

William A. Meissner, M.D., Chairman

March 12, 1971
Date

ADDENDUM

The names of individuals who contacted the Chairman or members of the Committee outside of the meeting and the substance of the conversations were, as follows:

1. Dr. Frank Stark of the American Cyanamid Company called the Chairman by telephone on 11/25/70 to ask if the Advisory Committee planned to have a meeting and, if so, about what date. He also asked if the American Cyanamid Company and Amchem Products, Inc. would be invited. The Chairman informed him that there would be a meeting about the middle of December and that they definitely would be invited to present data to the Committee.

2. On 12/7/70, Dr. Stark, representing the American Cyanamid Company, called the Chairman by telephone to request that representatives of the American Cyanamid Company and Amchem Products, Inc., be allowed to appear before the Committee on the afternoon of December 16 instead of the morning of December 17, as planned. The Chairman granted the permission for this change provided it would not interfere with the agenda or function of the meeting as far as the Secretariat was concerned. Permission was also granted to have the representatives of the two companies meet jointly with the Committee, rather than separately.

3. On 2/8/71 a reprint on Pesticide Residues in Total Diet Samples (V) by P. E. Corneliussen (1970) was received from C. Boyd Shaffer, Ph.D , American Cyanamid Company (R-19).

APPENDIX 1

EXHIBITS

E-1 Notice of cancellation of registration of certain products bearing directions for use on food in the absence of finite tolerances or exemptions (PR Notice 68-6, February 1, 1968).

E-2 Labeling of Amitrole products bearing food crop uses.

E-3 Petitions for an advisory committee filed in behalf of the registrants, March 13 and 14, 1968.

E-4 Federal Insecticide, Fungicide, and Rodenticide Act, 1964.

E-5 Rules governing the appointment, compensation, and proceedings of an advisory committee, and rules of practice governing hearings under the Federal Insecticide, Fungicide, and Rodenticide Act, August 29, 1969.

E-6 Interdepartmental coordination of activities relating to pesticides, by the Department of Agriculture, the Department of Health, Education and Welfare, and the Department of the Interior, 1964.

E-7 Statement by Arthur S. Felmming, Secretary of Health, Education, and Welfare, at news conference, November 9, 1959.

E-8 Department of Health, Education, and Welfare release announcing speed-up of cranberry analysis for aminotriazole, November 16, 1959.

E-9 Portion of statement showing scientific background for Food and Drug Administration action against aminotriazole in cranberries, November 17, 1959.

E-10 Department of Health, Education, and Welfare report on actions taken with respect to aminotriazole and stilbestrol, January 26, 1960.

E-11 "No residue" and "Zero tolerance" report by Pesticide Residues Committee, National Academy of Sciences, National Research Council, 1965.

E-12 Notice to manufacturers, formulators, distributors and registrants regarding abandonment of "Zero tolerance" and "No residue" concepts, with attached National Research Council Pesticide Residues Committee Report, April 13, 1966.

E-13 Interdepartmental referral comments from United States Public Health Service, regarding reregistration of Amitrol T, June 13, 1969.

E-14 Excerpts from the Report of the Secretary's Commission on Pesticides and their Relationship to Environmental Health, December, 1969.

APPENDIX 1

E-15 Letter from Amchem Products, Inc., with residue data regarding use of Amitrole on crop land, March 13, 1968.

E-16 List of products involved in the advisory committee proceedings.

APPENDIX 2

ADDITIONAL EXHIBITS

AE-1 Presentation of information on Amitrole to the Advisory Committee on December 16, 1970, by representatives of Amchem Products, Inc. and American Cyanamid Co.

AE-2 Chronology of Amitrole development and key registration actions.

AE-3 Statement by Dr. C. Boyd Shaffer, Director of Toxicology, American Cyanamid Company, before the Amitrole Advisory Committee--16 December, 1970.

AE-3a One-year status report to American Cyanamid Company. Two-year sub-acute dermal toxicity study on Amitrole 3-AT in Albino rats.

AE-3b IBT No. N7640 - two-year chronic inhalation toxicity study with Amitrole 3-AT in Albino rats.

AE-3c Project #16. Carcinogenesis assay studies (12/15/66).

AE-3d Project #16. Carcinogenesis assay studies (5/8/67).

AE-3e Letter of 10/24/68 to Dr. Harry W. Hays from C. Boyd Shaffer, Ph.D.

AE-3f Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note.

AE-3g Effect of Aminotriazole on thyroid function in the rat.

AE-3h Antithyroid effects of Aminotriazole.

AE-4 Statement by Dr. Robert M. Clyne, Corporate Medical Director, American Cyanamid Company, before the Amitrole Advisory Committee--16 December, 1970.

AE-5 Position statement of American Cyanamid Company and Amchem Products, Inc., regarding Amitrole registrations.

AE-6 Metabolism of Amitrole in excised leaves of Canada thistle ecotypes and bean.

AE-7 Influence of environmental and chemical factors on Amitrole metabolism in excised leaves.

AE-8 Guidelines for Selected Use of Amitrole (issued by the working group of the Subcommittee on Pesticides, President's Cabinet Committee on the Environment, February 4, 1970).

APPENDIX 2

AE-9 Statement by Mr. Richard J. Otten, Program Coordinator, State and Federal Labeling, Amchem Products, Inc., before the Amitrole Advisory Committee, 16 December, 1970.

AE-9a Some physiological and phytotoxicological properties of Amitrole.

AE-9b Pesticide residues in total-diet samples.

AE-9c Residues in food and feed. Assessments include raw food and feed commodities, market basket items prepared for consumption, meat samples taken at slaughter.

AE-9d Residues in food and feed. Pesticide residues in total diet samples (II).

AE-9e Residues in food and feed. Pesticide residues in total diet samples (IV).

AE-9f Letter of 5/29/59 to Mr. R. W. Gannon, Amchem Products, Inc., and Mr. F. Ray Barron, American Cyanamid Company, from F. J. McFarland.

AE-9g Letter of 1/23/68 to Amchem Products, Inc., from Harold G. Alford.

AE-9h Letter of 2/15/68 to Mr. R. J. Otten, Amchem Products, Inc., from Harold G. Alford.

AE-9i Amizine advertisement by Amchem Products, Inc.

AE-9j Weedazol advertisement by Amchem Products, Inc.

AE-9k Amitrol-T advertisement by Amchem Products, Inc.

AE-9l Weedazol advertisement by Amchem Products, Inc.

AE-10 Tests on mice for evaluating carcinogenicity.

APPENDIX 3

REFERENCES

R-1 Fang, S. C., George, M., and Yu, T. C.: Metabolism of 3-Amino-1,2,4-triazole-5-C^{14} by Rats, J. Agr. and Food Chem., 12:219-223, 1964.

R-2 Dalgaard-Mikkelsen, S. and Poulsen, E.: Toxicology of Herbicides, Pharm. Rev., 14:225-250, 1962.

R-3 Alexander, N. M.: Antithyroid Action of 3-Amino-1,2,4-triazole, J. Biol. Chem., 234:148-150, 1959.

R-4 Strum, J. M. and Karnovsky, M. J.: Aminotriazole Goiter. Fine structures and Localization of Thyroid Peroxidase Activity, Lab. Investig., 24:1-2, 1971.

R-5 Goodman, L. and Gilman, A.: The Pharmacological Basis of Therapeutics, New York: Macmillan Co., 1970.

R-6 Sinha, D., Pascal, R. and Furth, J.: Transplantable Thyroid Carcinoma Induced by Thyrotropin: Its Similarity to Human Hurthle Cell Tumors, Arch. Path., 79:192-198, 1965.

R-7 Herbicide Handbook of the Weed Science Society of America, 1967.

R-8 Carter, M. C.: "Amitrole," in Kearney, P. C. and Kaufmann, D. D.: Degradation of Herbicides, New York: Marcel Dekker, Inc., 1969, pp 187-206.

R-9 Sund, K. A.: Residual Activity of 3-Amino-1,2,4-triazole in Soils, J. Agr. and Food Chem., 4:57-60, 1956.

R-10 Ashton, F.M.: Fate of Amitrole in Soil, Weeds, 11:167-170, 1963.

R-11 Ercegovich, C. D. and Frear, D. E. H.: The Fate of 3-Amino-1,2,4-triazole in Soils, J. Agr. and Food Chem., 12:26-28, 1964.

R-12 MacRae, I. C. and Alexander, M.: Microbial Degradation of Selected Herbicides in Soil, J. Agr. and Food Chem., 13:72-76, 1965.

R-13 Kaufman, D. D., Plimmer, J. R., Kearney, P. C., Blake, J. and Guardia, F. S.: Chemical Versus Microbial Decomposition of Amitrole in Soil, Weed Sci., 16:266-272, 1968.

R-14 Plimmer, J. R., Kearney, P. C., Kaufman, D. D. and Guardia, F. S.: Amitrole Decomposition by Free Radical Generating Systems and Soil, J. Agr. and Food Chem., 15:996-1000, 1967.

APPENDIX 3

R-15 Riepma, P.: Preliminary Observations on the Breakdown of 3-Amino-1,2,4-triazole in Soil, Weed Res., 2:41-50, 1962.

R-16 Onley, J. H. and Storherr, R. W.: An Oregon Cranberry Bog Study for 3-Amino-1,2,4-triazole Residues, 1961-1962, Jour. A.O.A.C., 46:996-1001, 1963.

R-17 Leonard, O. A. and Weaver, R. J.: Absorption and Translocation of 2,4-D and Amitrole in Shoots of the Tokay Grape, Hilgardia, 31-327-368, 1961.

R-18 Federal Food, Drug, and Cosmetic Act, As Amended, U. S. Dept. Health, Ed. and Welfare, Public Health Serv., Food and Drug Administration, April, 1970.

R-19 Corneliussen, P. E.: Residues in Food and Feed. Pesticide Residues in Total Diet Samples (V), Pesticides Monitoring J., 4:89-92, 1970.

U. S. GOVERNMENT PRINTING OFFICE: 1972—484-486/265